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Optimization and characterization of controlled release pellets coated with an experimental latex: II. Cationic drug

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Abstract

The objective of the present study was to evaluate three process parameters for the application of an experimental latex to obtain multiparticulate controlled drug delivery of prazosin hydrochloride. A laboratory size fluidized bed coating machine (Uniglatt M-2817) was used to coat prazosin hydrochloride (cationic) loaded beads with the experimental latex to release an equivalent of 5 mg of drug in 24 h. A three factor-three level, face-centered cubic design was used to evaluate the effect of inlet air temperature, atomization pressure and spray rate on the cumulative percent released in 24 h with constraints at 6, 12 and 18 h, and the time for the release of 50% of drug (t_{50}). Contour and response surface plots were used to relate the independent and dependent variables. The optimization procedure predicted a maximum of 98% release in 24 h when the inlet air temperature, atomization pressure and spray rate were 45.11°C, 2.5 kp/cm^2 and 11.49 ml/min, respectively. The optimized beads prepared based upon the predicted values, yielded responses which were close to the predicted values. Further, the effect of solids content, coating volume and type of prazosin hydrochloride polymorph on its dissolution from coated beads have been evaluated. All the preparations were characterized by differential scanning calorimetry (DSC), scanning electron microscopy (SEM) and X-ray diffraction (XRD). The release kinetics from the optimized pellets were shown to follow the Higuchi square-root model.

Keywords: Controlled release; Coating; Latex; Optimization; Face-centered design; Prazosin hydrochloride; Characterization

1. Introduction

The preparation of a water-based coating dispersion of acrylate and methacrylate monomers (Ex-913-509-1291) and its application to obtain

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controlled release pellets of the anionic drug, ibuprofen, has been reported recently (Singh et al., 1995). Ibuprofen was chosen as a model because of its high dose requirement, anionic character and short half-life. The effect of formulation variables on the release of ibuprofen from coated pellets has been reported. The present study is directed towards the preparation of optimized controlled release beads of prazosin hydrochloride. The low dose requirements of prazosin hydrochloride and its cationic nature provide a suitable drug model to test the versatility of the experimental latex for controlled drug delivery. Further, the evaluation of process variables to obtain free flowing beads with a coherent film to provide a controlled drug delivery would be useful for its formulation. Prazosin hydrochloride [1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furanylcarbonyl)-monohydrochloride] is indicated in the treatment of mild to moderate hypertension. It is slightly soluble in water, very slightly soluble in alcohol, and has an apparent pKa of 6.5 in 1:1 water and ethanol solution (Groth and Lee, 1978). It is readily absorbed after oral administration. Peak serum levels are attained in 2–3 h and it has a half-life of 4–5 h (Parker, 1980). Its average dosing is 1–2 mg three times a day. Thus, its short half-life and increased dosing frequency suggest the need for a controlled delivery of prazosin for better patient compliance.

The objectives of the present study were to investigate the effect of process variables on the in-vitro release of prazosin from beads coated with the experimental latex and to characterize the optimized beads. Also the effect of polymorphic form, and formulation variables such as coating volume and solids content were studied.

1.1. Experimental design

A three-factor, three-level face-centered cubic design (Murray, 1994) was used to construct a second order polynomial model for the optimization process. This design is a three-level fractional-factorial experiment suitable for exploration of quadratic response surfaces. It is essentially a central composite design with the star points normally lying outside the region of interest brought in to lie on the boundary of the region of interest. This design provides an empirical mathematical model to describe the effect of process variables on the product characteristics. The model is of the form:

Table 1
Independent variables: factors and their levels for face-centered cubic design

Factors	Levels		
	−1	0	1
Atomizing pressure, kp/cm^2 (X_1)	1.5	2	2.5
Inlet air temperature, °C (X_2)	30	40	50
Spray rate, ml/min (X_3)	10	15	20

Table 2
Dependent variables and the constraints used

	Dependent variables/responses	Constraints
Y_1	Time in h for 50% of drug dissolution, t_{50}	$7 \geq Y_1 \leq 10$
Y_2	Cumulative % dissolved in 6 h	$35 \geq Y_2 \leq 55$
Y_3	Cumulative % dissolved in 12 h	$56 \geq Y_3 \leq 75$
Y_4	Cumulative % dissolved in 18 h	$76 \geq Y_4 \leq 85$
Y_5	Cumulative % dissolved in 24 h	$86 \geq Y_5 \leq 100$

Table 3
Composition of drug layering suspension/slurry

Ingredients	% w/w
Prazosin hydrochloride	3.34
Opadry II®	3.5
Kowets titanium dioxide	0.2
Talc	3.34
FDC lake dispersion (blue)	0.55
Distilled water	89.07

Table 4
Composition of seal coating solution

Ingredients	% w/w
Opadry II®	4.45
Talc	4.45
Tween 20	0.90
Kowets titanium dioxide	0.30
FDC Lake dispersion (blue)	0.75
Distilled water	89.15

Table 5
Experimental runs and observed responses (randomized)

Run #	Controlled factors			Measured responses				
	X_1	X_2	X_3	Y_1	Y_2	Y_3	Y_4	Y_5
1	−1	−1	−1	6.85	47.18	68.92	82.54	99.88
2	1	−1	−1	3.70	66.26	83.79	89.33	99.15
3	−1	1	−1	15.70	27.48	46.04	53.86	65.77
4	1	1	−1	7.10	43.89	66.65	76.96	92.63
5	−1	−1	1	2.30	80.49	93.27	97.44	98.78
6	1	−1	1	2.85	72.03	83.70	87.63	99.29
7	−1	1	1	6.25	49.69	67.19	86.89	98.72
8	1	1	1	7.60	43.64	67.31	88.97	99.80
9	−1	0	0	7.25	48.84	66.78	87.34	98.37
10	1	0	0	8.45	38.59	63.75	89.16	99.97
11	0	−1	0	5.40	53.27	77.22	90.13	98.80
12	0	1	0	12.70	31.71	49.27	69.14	70.13
13	0	0	−1	6.00	51.09	64.25	79.94	88.38
14	0	0	1	8.70	41.31	61.66	76.75	85.57
15	0	0	0	7.30	43.50	65.26	81.90	97.20
16	0	0	0	8.01	38.56	62.70	76.96	86.40
17	0	0	0	7.47	43.37	70.90	91.52	99.19

$$Y = a_0 + a_1X_1 + a_2X_2 + a_3X_3 + a_4X_1X_2 + a_5X_2X_3 + a_6X_1X_3 + a_7X_1^2 + a_8X_2^2 + a_9X_3^2 + E$$

Where a_1–a_9 are the coefficients of the respective variables and their interaction terms, and E is an error term. Preliminary studies provided the levels used for studying the effect of process variables. The factors selected were atomization pressure (X_1), inlet air temperature (X_2) and spray rate (X_3). An orthogonal design was used such that the factor levels were evenly spaced and coded for low, medium and high setting as −1, 0 and 1, respectively. Table 1 summarizes the factors and their levels. Table 2 shows the responses studied and the constraints that were placed on the responses.

2. Materials and methods

2.1. Materials

Experimental latex dispersion (Ex-913-509-1291) was received from BF Goodrich Co. Prazosin hydrochloride (α form; lot # R84112-04021-05) was received as a gift from Pfizer, (Groton, CT) and β and polyhydrate forms were gifts from BASF (City, NJ). Nupareil seeds (mesh 18/20, Ingredient Technology, NJ) were used to prepare the pellets. Opadry II® (YS-7472, Colorcon, PA) was used for seal coating. Triethyl citrate (Morflex Chemical, Greensboro, NC) was used as a plasticizer. Titanium dioxide was used as opacifier (Warner Jenkins). Talc was purchased from Spectrum Chemical Company. All other chemicals were of reagent grade and used as received. Water used in all experiments was deionized and distilled.

2.2. Methods

2.2.1. Drug layering

Approximately 1000 g of Nu-pareil sugar beads (mesh # 18/20) were used as initial cores to achieve 80% or greater drug loading. Table 3 shows the coating composition used for drug layering. Prazosin hydrochloride was passed through US sieve # 30 and was mixed with water. OpadryII® was used as a binder and talc was used as an anti-adherent. Required amounts of Tween 20, titanium dioxide and FDC approved blue lake dispersion were added. The slurry was finally

Table 6
Summary of regression results for the measured responses

Y	b_0	b_1	b_2	b_3	b_4	b_5	b_6	b_7	b_8	b_9	r^a	Confidence (%)[b]
Y_1	—[c]					0.68					0.82	94.6
Y_2	131.41					−2.50				0.26	0.87	99.5
Y_3	163.74					−2.25					0.89	99.5
Y_4	161.06	−94.81			0.71	−1.88	0.08	24.91			0.83	99.5
Y_5	230.46	−159.18			0.70		0.10	38.82			0.75	85.9

[a] Multiple correlation coefficient.
[b] Confidence regression equation is non zero.
[c] Blanks indicate that regression confidence for the factor was less than 75%.

mixed for 3–4 h prior to use in a high speed mixer, and filtered through a 40 mesh screen filter.

A laboratory size Uniglatt fluidized bed coating machine (Glatt, model # 2817) was used for coating the drug suspension using a 1.2 mm Wurster insert. The flow rate of the suspension was maintained constant at 5 ml/min which prevents the agglomeration of beads during the coating process. The inlet air temperature was 45°C and the atomizing air pressure was 3 kg/cm^2. The air flap was kept between 35–60° to achieve good drying efficiency. The filter assembly was shaken every 15–20s for 5s. After drug layering, the beads were dried for 15 min at 45°C in the coating chamber. These were collected in a tray and dried at 37°C in an oven for 24 h.

Table 7
Residual table for predicted response Y_5

Run #	Observed	Predicted	Residuals
1	99.88	99.64	0.24
2	99.15	104.60	−5.45
3	65.77	68.56	−2.79
4	92.63	87.60	5.03
5	98.78	102.78	−4.00
6	99.29	95.47	3.82
7	98.72	92.24	6.48
8	99.80	99.01	0.79
9	98.37	98.29	0.08
10	99.97	104.16	−4.19
11	98.80	93.41	5.39
12	70.13	79.64	−9.51
13	88.38	85.40	2.98
14	85.57	92.67	−7.10
15	97.20	91.52	5.68
16	86.40	91.52	−5.12
17	99.19	91.52	7.67

2.2.2. Seal coating

Opadry II® was used as the permeable seal coating polymer. Preliminary studies indicated that the seal coating did not hinder the diffusion of the drug. Table 4 shows the seal coating composition used. Seal coating was applied to the layered pellets prior to the latex coating to minimize leaching of the drug into the latex membrane and also, to prevent mechanical abrasion of the layered drug during the coating operation.

2.2.3. Controlled release coating

Preliminary experiments indicated that a volume of 75 ml of latex coating (15% w/w weight gain) provided a uniform coating. Based on the earlier study (Singh et al., 1995) the total solids of the latex was maintained at 11.06% w/w and the plasticizer (triethyl citrate) concentration was 26.59% w/w. For the three factors at three levels each, 17 batches were prepared. The process parameters used for each batch are listed in Table 5.

2.2.4. Sieve analysis

After coating the 17 batches, beads were subjected to sieve analysis using a nest of US standard sieves (10, 12, 16, 18, 20, 25, 30 mesh). For each batch, a weighed amount of beads was placed on a Retsch sieve shaker at a fixed setting of 20 for 5 min. Pellets collected on top of each size range were weighed. All fines and agglomer-

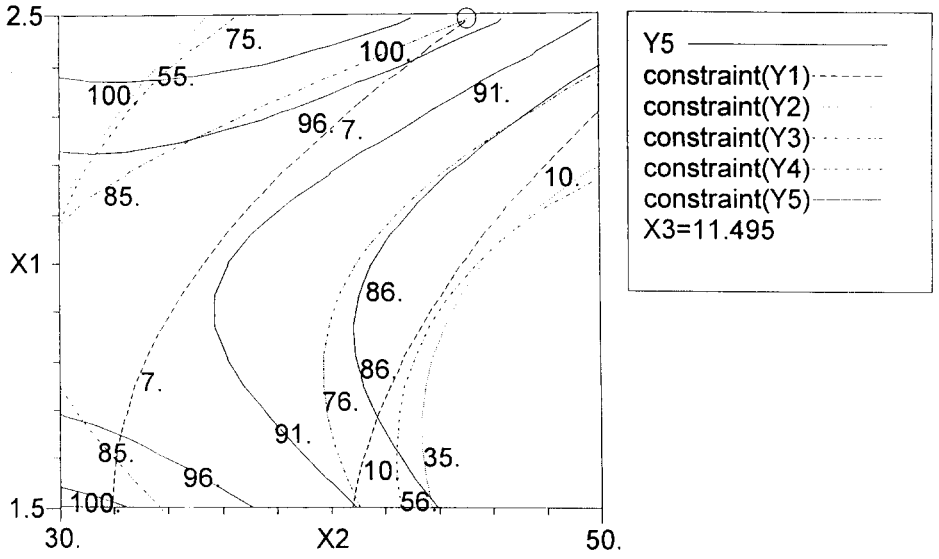

Fig. 1. Contour plot showing the effect of atomizing pressure (X_1) and inlet air temperature (X_2) on the response Y_5.

ates were discarded. The fractions of beads remaining between sieve #'s 16–25 were collected and used for further characterization of the formulation.

2.2.5. Content uniformity

An accurately weighed sample of the coated pellets (100 mg) from all the batches was dissolved in methanoloic solution of 0.01 N HCl, filtered and analyzed spectrophotometrically for prazosin content at 331.5 nm. A calibration curve of standard concentrations of prazosin hydrochloride in methanoloic solution of 0.01 N HCl was used. All experiments were performed in triplicate.

2.2.6. Dissolution studies

Coated beads equivalent to 5 mg of prazosin were used for determining the in-vitro release of the drug. The U.S.P. Paddle Apparatus was used with 900 ml of 0.1 N HCl containing 3% sodium lauryl sulfate (pH 1.45) at 37°C and 100 rpm. Samples (5 ml) were withdrawn at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 18 and 24 h and assayed spectrophotometrically at 332 nm. From the absorbance values, the cumulative percent of prazosin released was calculated. All the experiments were performed in triplicate.

2.2.7. Infrared spectroscopy

Infrared spectra of the pure drug (three polymorphs), excipients and the optimized batch were determined from KBr pellets using a FT-IR, model 400D (Nicolet Analytical Instruments) attached to an OMNIC software. The scanning range used was 4000 to 400 cm^{-1}.

2.2.8. X-ray diffraction study

Qualitative and quantitative X-ray diffraction (XRD) studies were performed using a Philip's X-ray diffractometer, Model 1840. Measurements were carried out at 40 kV and 35 mA current at a continuous scan rate of 1s per step. Finely ground samples were scanned from 0–45° 2θ. Diffractogram of pure prazosin hydrochloride was used as a reference for qualitative studies. In the quantitative studies a standard plot of the peak height ratio (I/I_0) of pure prazosin hydrochloride to internal standard, sodium chloride, was constructed by the procedure reported earlier (Kislalioglu et al., 1991). The degree of crystallinity was estimated using this plot.

2.2.9. Differential scanning calorimetry (DSC)

DSC scans were performed using a Shimadzu DSC-50 Thermal Analyzer to obtain the melting endotherms of pure prazosin hydrochloride (three

different polymorphs), Opadry, latex and the optimized formulations. The instrument was calibrated using indium standards. Approximately 3 mg of each sample was weighed into small aluminum pans. Samples were heated from 150–300°C at a rate of 10°C per min in an atmosphere of nitrogen. Thermograms were normalized and autoscaled before overlapping.

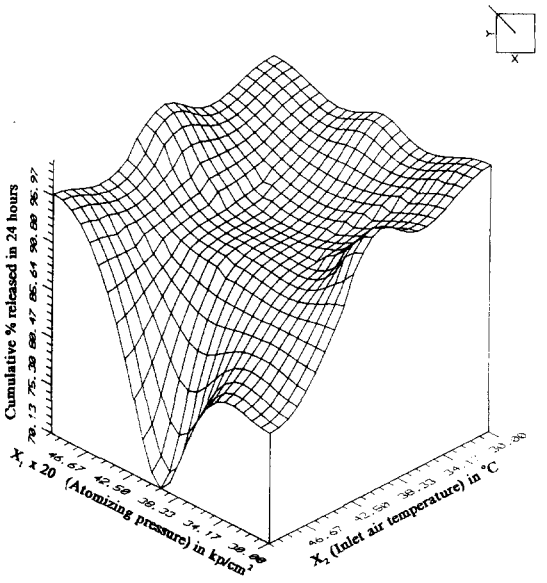

Fig. 2. Response surface plot (3D) showing the effect of atomizing pressure (X_1) and inlet air temperature (X_2) on the response Y_5.

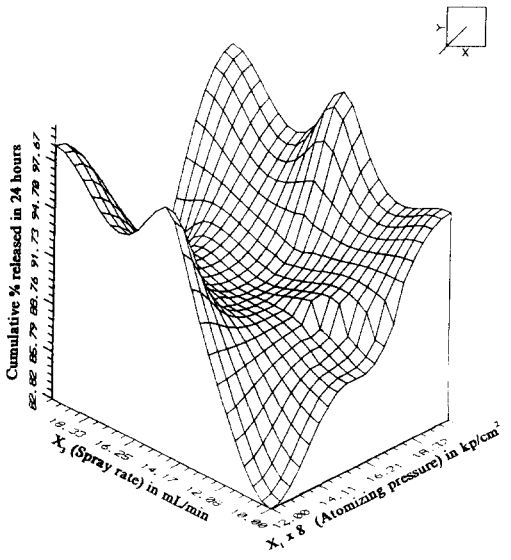

Fig. 3. Response surface plot (3D) showing the effect of atomizing pressure (X_1) and spray rate (X_3) on the response Y_5.

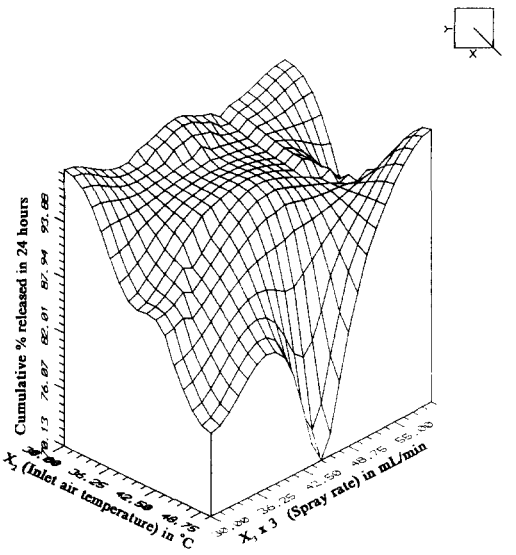

Fig. 4. Response surface plot (3D) showing the effect of inlet air temperature (X_2) and spray rate (X_3) on the response Y_5.

Table 8
Responses after maximizing

Responses	Predicted	Observed
Y_1	6.99	8.19
Y_2	44.73	40.48
Y_3	67.63	67.85
Y_4	85.00	88.82
Y_5	97.67	98.84

2.2.10. Scanning electron microscopy (SEM)

The surface topography of the optimized batch was examined under a Phillips model 505 SEM. The optimized beads were loaded on studs and sputter coated with gold for 105 s at 20 mA under a pressure of 0.1 Torr. The coated beads were scanned and the micrographs were examined for the effect of process variables on the surface morphology of the latex coating. Pictures of the intact bead and a cross section were taken to determine the integrity of the film.

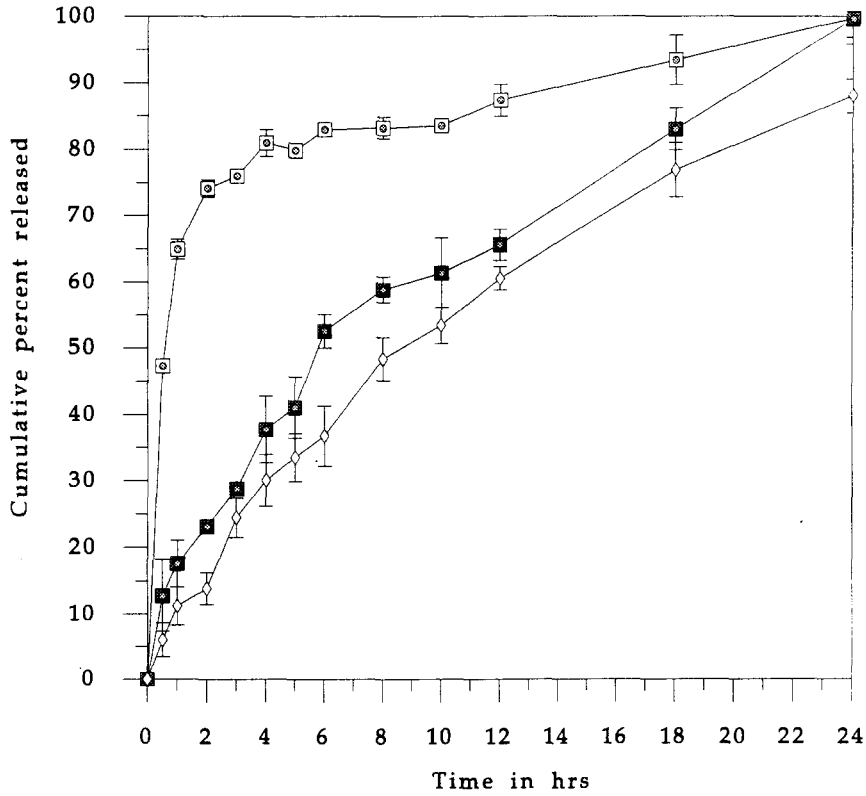

Fig. 5. Dissolution profiles of prazosin hydrochloride from beads coated with the experimental latex (75 ml) showing the effect of solids content on the release (open box with circle) 5%; (filled box with circle) 10%; and (diamond) 15%.

3. Results and discussions

Table 5 shows the experimental design in the randomized form and the responses observed. For each dependent variable, the data for the t_{50} responses and the cumulative percent dissolved at 6, 12, 18, 24 h were used to generate appropriate regression models using a statistical package, X-Stat 2.1® (Murray, 1994). A summary of the regression analysis is shown in Table 6. The table shows factors which have a significant effect on the dependent variable Y. Similar to the reported studies, the estimated coefficients for variables with regression confidence greater than 75% were considered to have a significant effect on the particular response (Khattab et al., 1993). The less significant terms were removed from the equations.

The resultant equations are shown below:

$$Y_1 = -5.85 + 4.47X_1 + 0.28X_2 + 0.24X_3 - 0.12X_1X_2 + 0.68X_1X_3 - 2.95X_1^2 - 0.05X_3^2 \quad (1)$$

$$Y_2 = 131.41 - 22.42X_1 - 2.7X_2 - 0.08X_3 - 2.5X_1X_3 - 0.04X_2X_3 + 15.58X_1^2 + 0.03X_2^2 + 0.26X_3^2 \quad (2)$$

$$Y_3 = 163.74 - 44.18X_1 - 3.52X_2 + 3.35X_3 + 0.39X_1X_2 - 2.24X_1X_3 + 16.76X_1^2 + 0.02X_2^2 + 0.07X_3^2 \quad (3)$$

$$Y_4 = 161.06 - 94.81X_1 - 1.41X_2 + 6.09X_3 + 0.71X_1X_2 - 1.88X_1X_3 + 0.08X_2X_3 + 24.91X_1^2 - 0.02X_2^2 - 0.15X_3^2 \quad (4)$$

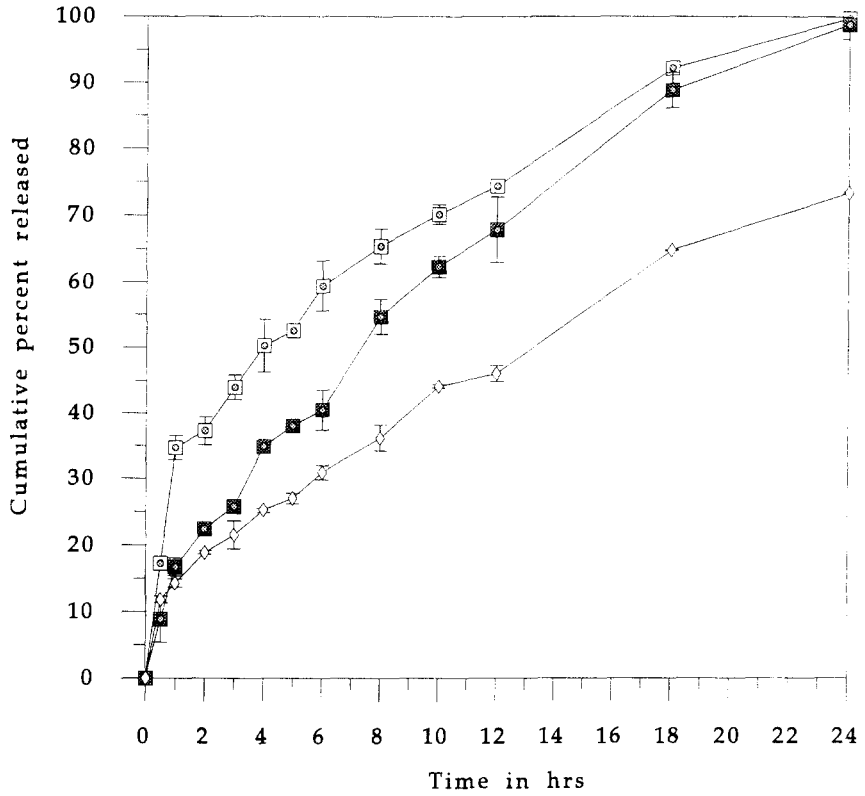

Fig. 6. Dissolution profiles of prazosin hydrochloride from beads coated with the experimental latex (11.06% w/w solids) showing the effect of volume of coating applied on the release (open box with circle) 50 ml; (filled box with circle) 75 ml; (diamond) 100 ml.

$$Y_5 = 230.46 - 159.18X_1 + 0.36X_2 + 2.06X_3 + 0.70X_1X_2 - 1.23X_1X_3 + 0.10X_2X_3 + 38.82X_1^2 - 0.05X_2^2 - 0.10X_3^2 \quad (5)$$

The coefficients of the X's in the above equation are corrected to two decimal places. Eqs. (1)–(5) represent the quantitative effect of the process variables on the five responses $Y_1 - Y_5$, respectively. The values of the coefficients $X_1 - X_3$ relate to the effects of these variables on the corresponding response. The coefficients with more than one factor term represent the interaction terms and coefficients with higher order terms indicate the quadratic (non-linear) nature of the relationship. The values of $X_1 - X_3$ were substituted in Eqs. (1)–(5) to obtain the theoretical values of $Y_1 - Y_5$. The theoretical (predicted) values were compared with the observed values and were found to be in good agreement. The observed, predicted, and the residual values for the dependent variable Y_5 are shown in Table 7.

To understand the relationship between the dependent and the independent variables, two and three dimensional plots for the measured responses were obtained based on the model. Fig. 1 is a representative contour plot which shows the effect of X_1 and X_2 on Y_5. The constraints for $Y_1 - Y_4$ are shown by the different type of contour lines used. These are listed in Table 2. The maximized point is indicated by a small circle. Fig. 2 is the corresponding response surface plot. It shows that at lower inlet air temperature (X_2), the increased dissolution with an increase in atomizing pressure from 1.5 to 2.5 kp/cm^2 is less pronounced than at higher inlet air temperature. This is probably due to the inability of latex to exceed the MFT (minimum film-forming temperature) which

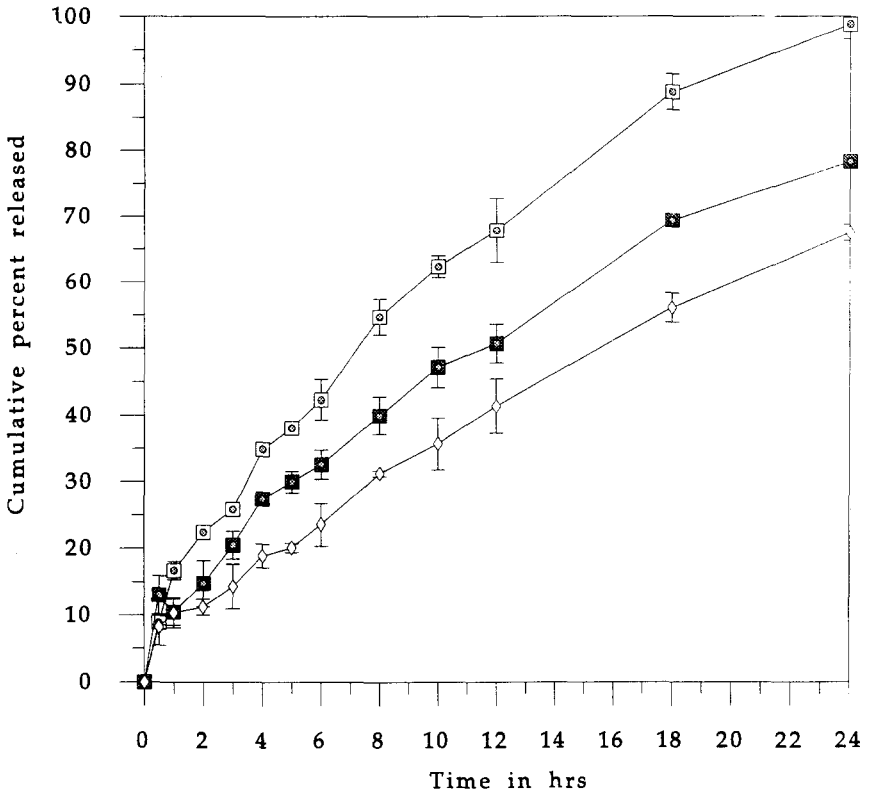

Fig. 7. Dissolution profiles of prazosin hydrochloride from beads coated with the experimental latex showing the effect of polymorph type on the release (open box with circle) prazosin α form; (filled box with circle) prazosin β form; (diamond) prazosin polyhydrate.

is required for the complete coalescence of the latex on the beads for the formation of a coherent film. Ideally, the inlet air temperature should be above the T_g (glass transition temperature) of the polymer composite. This is because of a coherent film formation at higher inlet temperature as it exceeds the T_g of the latex. Further, atomizing pressure is known to influence the droplet size and the uniformity of the coating solution (Ghebre-Sellassie, 1994).

Fig. 3 is the response surface plot which shows the effect of X_1 and X_3 on the response Y_5. At higher atomization pressure (X_1), the increase in the dissolution is less pronounced with an increase in spray rate than at lower atomization pressure. Also, at a higher spray rate the change in percent release is greater with an increase in atomization pressure than at a lower spray rate. Thus, at higher pressure the dissolution does not change appreciably with an increase in spray rate. However, at lower atomizing pressure the percent dissolved increases considerably with an increase in spray rate, because it leads to agglomeration and nonuniform coating distribution. Similarly, a high spray rate leads to agglomeration and uneven coating distribution while a lower spray rate provides better coating distribution uniformity (Ghebre-Sellassie, 1994).

Fig. 4 depicts the response surface plots which shows the effect of X_2 and X_3 on the response Y_5. At a higher spray rate (X_3), the change in the dissolution with an increase in inlet air temperature is uncorrelated while at a lower spray rate the dissolution decreases with an increase in inlet air temperature. Higher inlet air temperature helps in the formation of coherent film due to the coalescence of the latex above its MFT (Ghebre-Sellassie, 1994). At lower air temperature, the

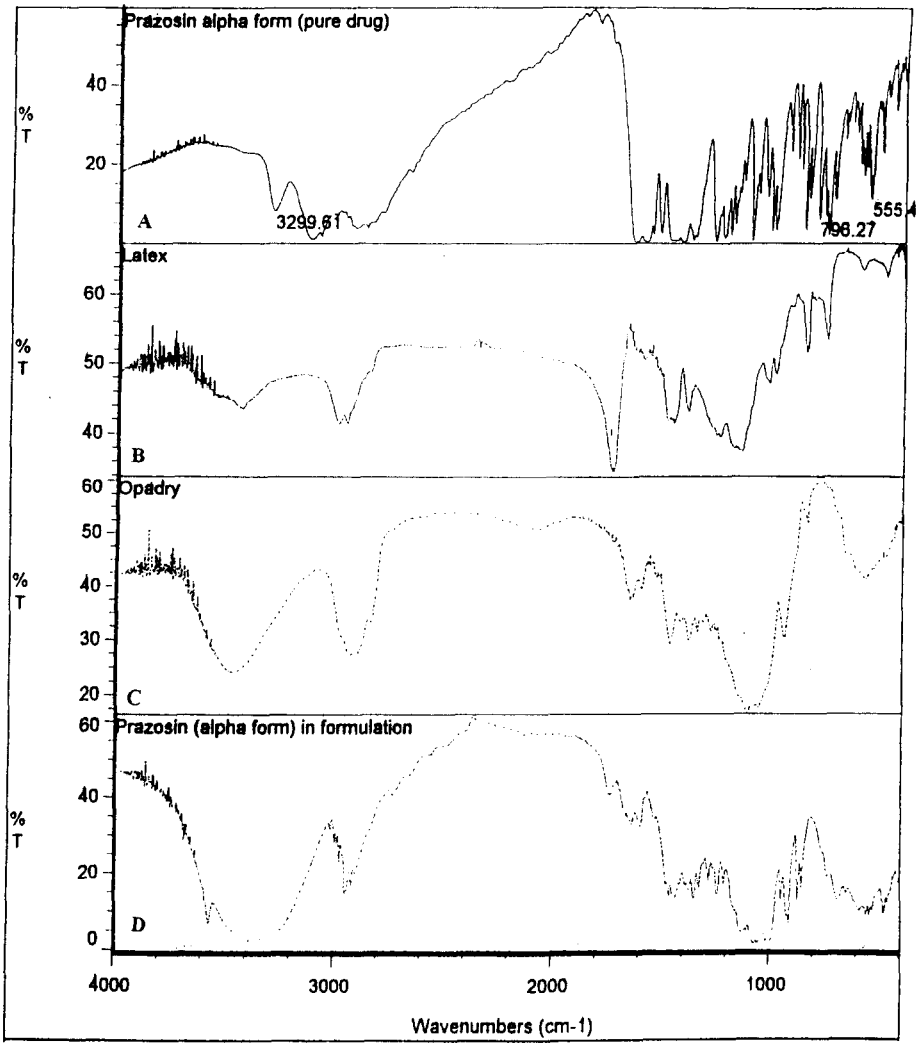

Fig. 8. Overlay of IR spectra of (A) prazosin hydrochloride α form; (B) latex; (C) opadry; (D) prazosin α in formulation.

increase in dissolution with an increase in spray rate is less pronounced than at higher inlet air temperature. The lower temperature prevents formation of a coherent film below the MFT of the latex and therefore, a change in spray rate does not have a significant effect on the dissolution. However, at higher inlet air temperature, increasing the spray rate results in agglomeration problems and the uniformity of coating distribution is less, although the high temperature influences the formation of a coherent film.

After generating the polynomial equations to relate the dependent and the independent variables, the process was optimized for the response Y_5. Optimization involves maximizing or minimizing a certain response with/without constraints. In this study, optimization was performed with constraints at Y_1, Y_2, Y_3 and Y_4 to maximize the response Y_5, i.e. cumulative percentage released in 24 h. The optimization procedure generated a maximum of 98% drug release after a period of 24 h. The theoretical levels of X_1, X_2 and X_3 which maximize Y_5 were 2.5 kp/cm^2, 45.11°C and 11.49

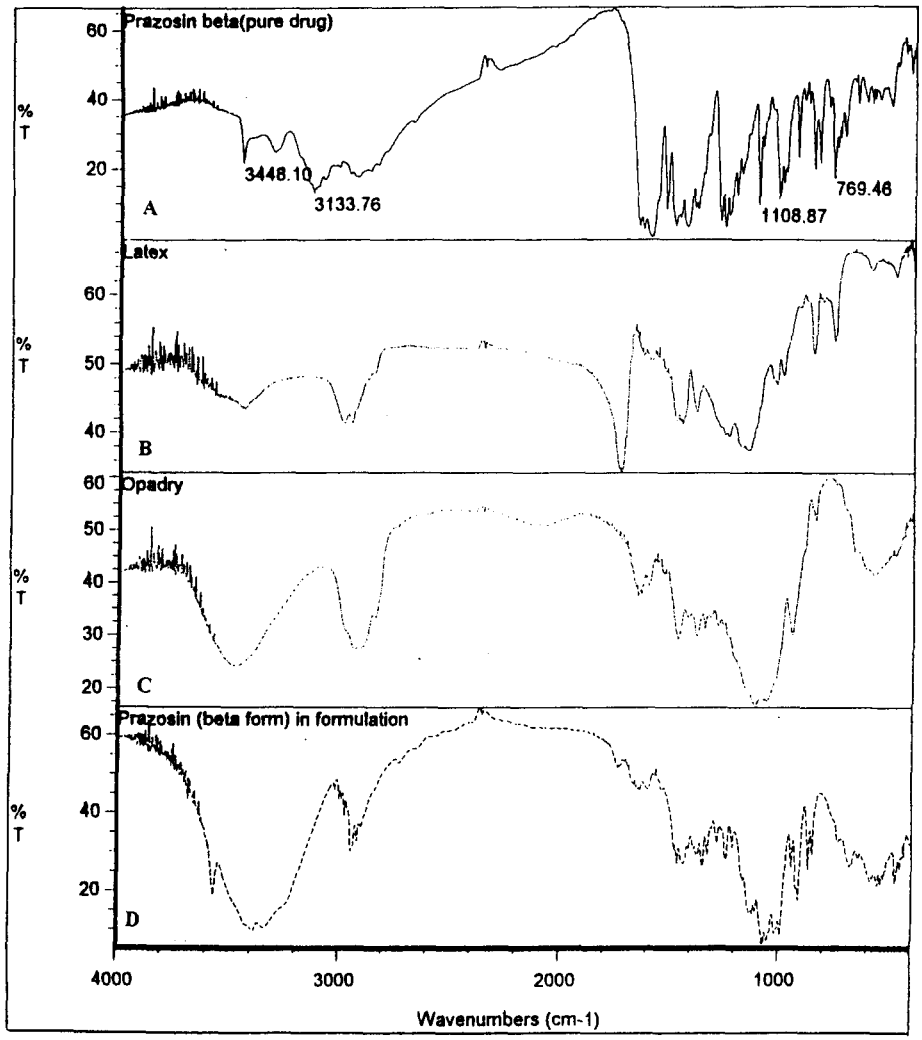

Fig. 9. Overlay of IR spectra of (A) prazosin hydrochloride β form; (B) latex; (C) opadry; (D) prazosin β in formulation.

ml/min, respectively. To validate the optimization procedure, a fresh batch of prazosin hydrochloride loaded beads were coated with 75 ml of the latex (11.06% w/w), plasticized with triethyl citrate (26.59% w/w) using the above conditions of the independent variables. This batch provided 98.70% release in a 24 h period. Table 8 illustrates the predicted and the observed responses for the optimized formulation.

The effect of formulation variables such as the latex solids content and the volume of coating applied were performed with the instrumental conditions set at levels obtained by the optimization procedure. As is evident from Fig. 5, the increase in solids content decreases the release. Thus, a higher concentration of polymer causes relatively more retardation in drug release. Fig. 6 shows the effect of volume of coating applied on the release from prazosin loaded beads at a fixed solid content of 11.06% w/w. The higher coating volume applied increases the thickness of the membrane and also the overall concentration of the polymer and thus causes a relatively higher retardation in release.

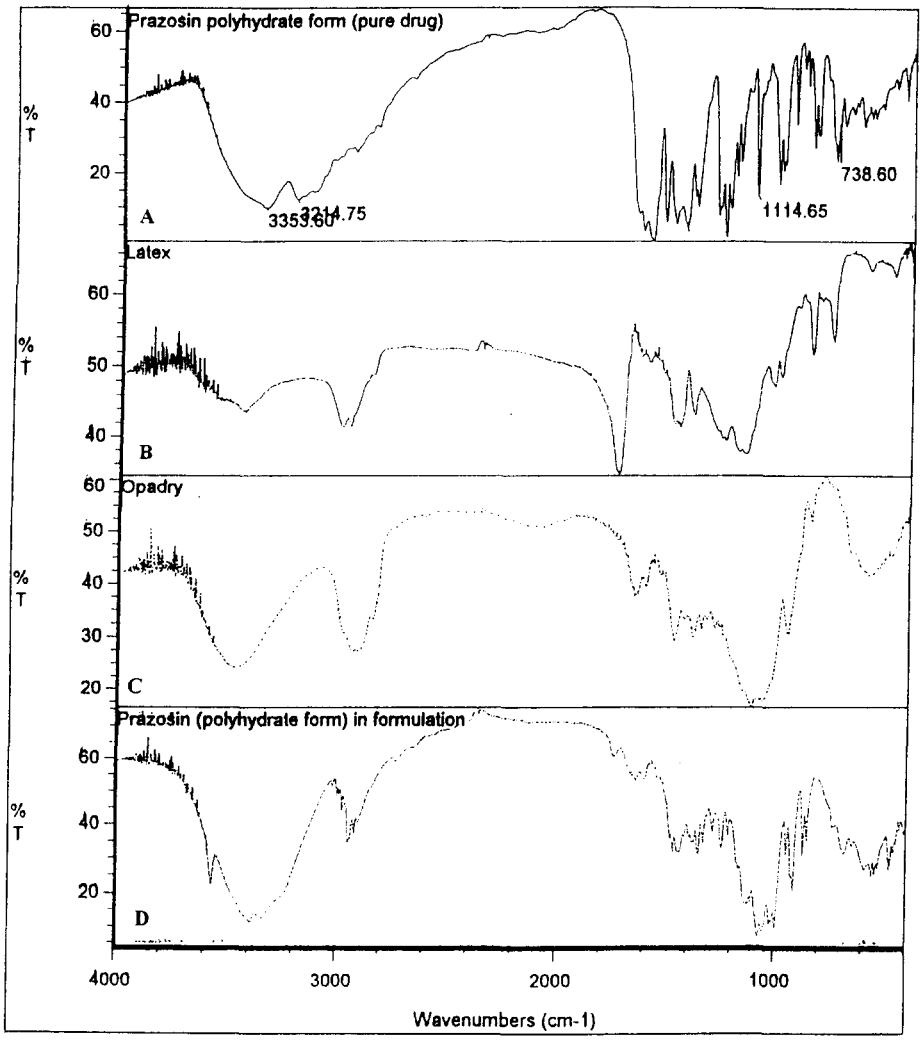

Fig. 10. Overlay of IR spectra of (A) prazosin hydrochloride polyhydrate form; (B) latex; (C) opadry; (D) prazosin polyhydrate in formulation.

A comparative evaluation of the effect of three polymorphic forms of the drug on the release from coated beads was performed using α, β and polyhydrate forms of prazosin hydrochloride during drug layering. The α form was used for the optimization study. The drug loaded beads were coated under the same process and formulation parameters as the optimized formulations. Fig. 7 shows the comparative dissolution profiles of beads coated with these polymorphic forms of the drug. The α form shows the highest dissolution rate while the polyhydrate form shows the slowest dissolution rate. The dissolution of prazosin hydrochloride from the formulation is related to its solubility or crystallinity of the polymorphic form in the formulation. The α form is anhydrous, and is the stable polymorph. It has 0.5–1.5% w/w of water at 37°C/75% R.H. The polyhydrate form is crystalline, and has 8–15% w/w of water. The β form is very hygroscopic and unstable (Bianco, 1976). The profiles shown in Fig. 7 clearly indicate a decrease in the dissolution with an increase in

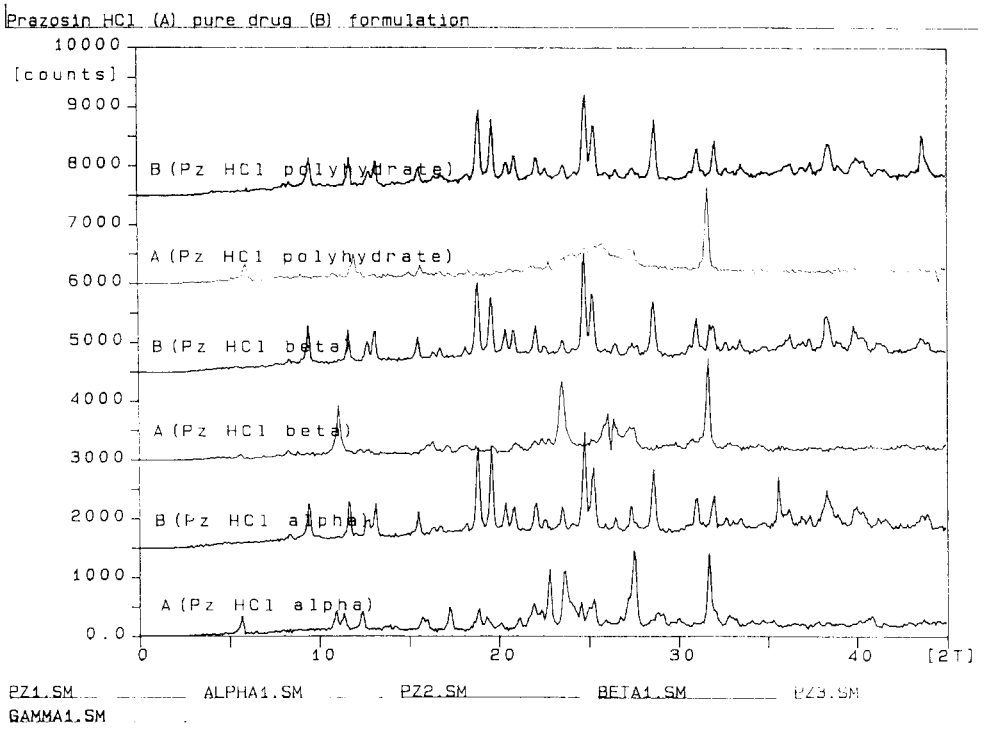

Fig. 11. Qualitative X-ray diffraction pâtterns of three polymorphs of prazosin hydrochloride (A) pure drug; (B) optimum formulation.

the crystalline polymorphic form of the drug. Also, these results correlate well with the powder dissolution and intrinsic dissolution rates of the polymorph (Bianco, 1976).

FTIR spectra of the pure drug (three polymorphic types), latex, Opadry® and their optimized formulations are shown in Figs. 8–10, respectively. Characteristic absorption stretch for C=O group at 1650 cm^{-1} and broad bands between 3000 and 3500 cm^{-1} for C–H stretch are observed. Also, the latex showed characterestic peak at 1700 cm^{-1} typical for C=O stretch for carbonyl compounds. The finger print region IR spectra showed a characteristic sharp peak at 765 cm^{-1} for the α form and at 770 cm^{-1} for the β form. Similarly, the polyhydrate form showed a charac-

Table 9
Peak intensity ratios of drug and optimum formulation with sodium chloride (Int. Std.)

Sample	I/I_0		2θ		d values		I/I_0 all peaks
	P_1^a	P_2^a	P_1^a	P_2^a	P_1^a	P_2^a	
Pure drug(α form)	0.79	1.03	23.65	27.49	3.75	3.24	6.05
Formulation (α form)	0.80	0.80	23.48	27.33	3.78	3.26	19.16
Pure drug (β form)	0.53	0.77	11.10	23.48	7.95	3.78	3.55
Formulation (β form)	0.87	0.68	11.70	23.48	7.55	3.78	18.38
Pure drug (polyhydrate form)	0.30	0.42	11.96	25.79	7.39	3.45	4.89
Formulation (polyhydrate form)	0.78	1.26	11.79	25.27	7.49	3.51	16.24

[a] P_1 and P_2 are specific peaks for the respective polymorphs.

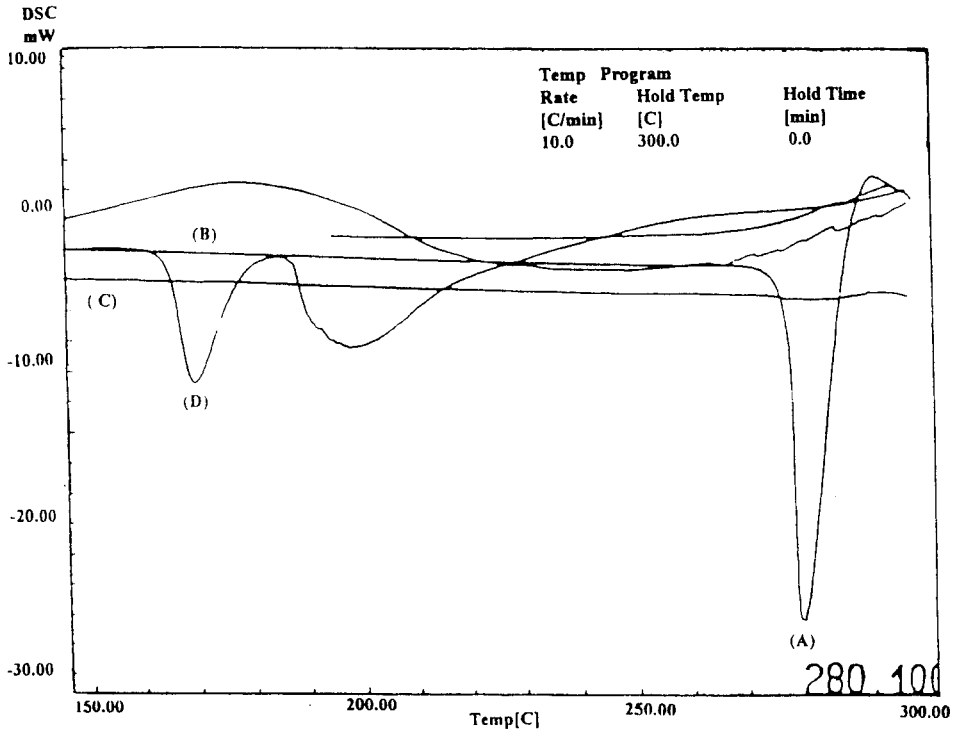

Fig. 12. Overlay of DSC thermograms of (A) prazosin hydrochloride α form pure drug; (B) opadry; (C) latex; (D) prazosin hydrochloride α form in formulation.

teristic peak at 1260 cm^{-1}, broad peak at 770 cm^{-1} and a doublet at 1000 cm^{-1}. In comparison with the pure polymorph, the finger print region of the spectra for the formulations of all the three polymorphs showed a considerable shift and disappearance of characteristic peaks of the drug suggesting an interaction between the drug and the latex.

X-ray diffraction patterns of the three different polymorphs of prazosin hydrochloride are shown in Fig. 11. A comparison between the diffraction patterns of the pure drug (A) and their respective formulation (B) for each polymorph suggests an increase in peak intensity of the formulations as compared with the pure drug. This effect was more pronounced with the polyhydrate form. The appearance of new doublet peaks at 25.2° 2θ for prazosin hydrochloride formulation B (α form) suggests some transformation of α form to polyhydrate form. Similarly, the appearance of new peaks in the patterns of prazosin hydrochloride formulation B (β form) at 25.2° 2θ, a characteristic doublet of polyhydrate form and also at 9.4 and 27.4° 2θ, characteristic peaks of α-form, suggests changes in polymorphic form in the formulation. The appearance of new peaks at 9.4° 2θ in the patterns of prazosin hydrochloride formulation B (polyhydrate form) also suggests partial reversion to α form in the formulation. To study the quantitative change in the degree of crystallinity, a standard curve was plotted for peak intensity ratio of pure polymorph (I) to internal standard (I_0) vs drug concentration. Sodium chloride was used as the internal standard. Physical mixtures of the drug and dried ground latex with internal standard were run and peak intensity, the angle '2θ' and the 'd' values were obtained. A linear relationship of I/I_0 was observed with increasing drug concentration ($r = 0.99$). Two characteristic peaks of each polymorphs were used for quantification, since they were most sensitive to changes in drug concentration (Karnachi et al.,

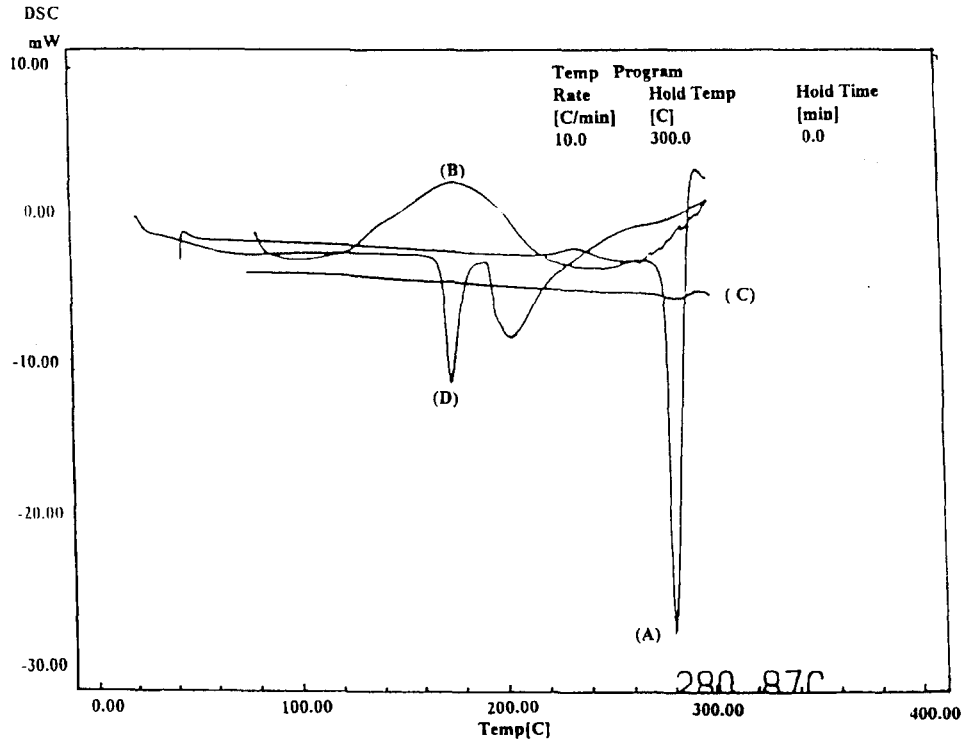

Fig. 13. Overlay of DSC thermograms of (A) prazosin hydrochloride β form pure drug; (B) opadry; (C) latex; (D) prazosin hydrochloride β form in formation.

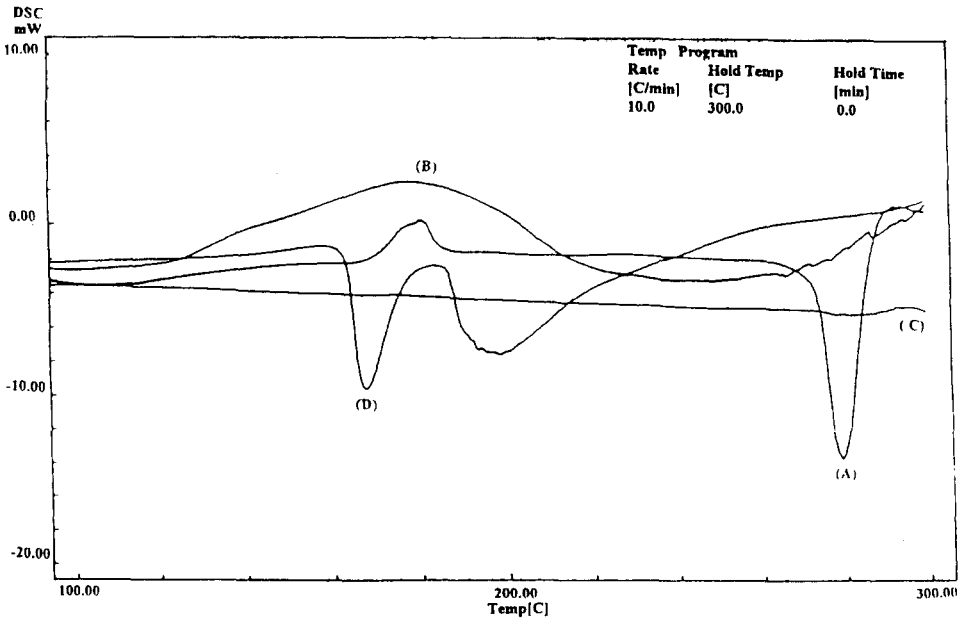

Fig. 14. Overlay of DSC thermograms of (A) prazosin hydrochloride polyhydrate form pure drug; (B) opadry; (C) latex; (D) prazosin hydrochloride β form in formulation.

1995). Also, the overall peaks for pure drug and the drug in the formulation were integrated to estimate the degree of crystallinity. Table 9 shows the characteristic peaks of the polymorphs in both the pure drug and formulation and their relative peak intensity ratios. The I/I_0 values in Table 9 show an increase in peak intensity ratio (I/I_0) for the formulations, except for the α form. However, integration of all the peaks for the drug and formulation as shown in Table 9, revealed a definite increase in crystallinity in all the formulations. The d-values changed considerably for the polyhydrate form and relatively less for both the β and α forms of the drug. These results confirm the IR findings of an interaction between prazosin hydrochloride and the latex.

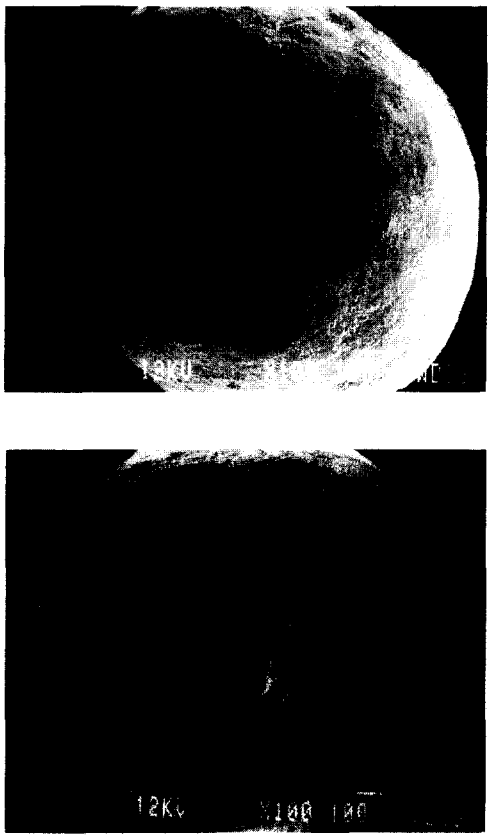

Fig. 15. SEM pictures of beads coated with the experimental latex (top) surface structure (bottom) cross section of the coated beads.

Table 10
Least-square parameters applied to dissolution of the optimized formulation

Dissolution models	Dissolution rate constant (k)	r^2
Higuchi's square root model	21.3084	0.9937
Baker-Lonsdale model	0.0171	0.9656
Bamba's model	0.1200	0.7123
First-order model	0.1596	0.9503
Hixon-Crowell cube root model	0.0282	0.7740
Two-third model	0.0363	0.9220

DSC scans of the pure drug (three polymorphs), latex, Opadry® and their corresponding formulations were obtained. The α form showed a sharp melting peak at 280.10°C. The melting endotherm of the β form was at 280.87°C and the polyhydrate form showed a weak exotherm at 180.73°C, and an endotherm at 279.41°C. Opadry® has a melting point at 52°C and thus did not show any melting endotherm within the range of heating for the DSC scans. Interestingly, the DSC scans of the optimum formulation of each polymorphic form of the drug showed a clear shift in the characteristic peak in comparison with the pure form of the drug. Figs. 12–14 show the corresponding overlay of the DSC thermograms of α form, β form and the polyhydrate form, respectively. Clearly, all the DSC figures reveal the interaction between prazosin and the coating excipients.

SEM pictures of the optimized beads of prazosin in Fig. 15 show a uniform and intact coating of the latex. The surface structure appeared to be rough due to the presence of anti-adherent on the surface. The cross-section of the beads show the porous nature of the core and a distinct layer of the coated film at the exterior. Thus, a coherent film was formed on the drug layered beads which was responsible for controlling the release.

Various dissolution models were used to fit the dissolution kinetics of the pellets from optimized prazosin hydrochloride beads coated with the polymer latex. Table 10 shows the least square parameters of the various model equations applied. The Higuchi square root model (Higuchi, 1963) appears to provide the best correlation.

4. Conclusions

The process variables, inlet air temperature, atomization pressure and spray rate affected the release of prazosin hydrochloride from pellets coated with insoluble latex. The effect of these variables could be predicted quantitatively using a set of polynomial equations. These equations were used to predict optimum levels of the desired release by using the predicted levels of process parameters. The optimum batch prepared according to the predicted levels provided responses which were similar to the predicted levels. The experimental latex was useful in developing a controlled delivery of the cationic drug, prazosin hydrochloride. A comparative evaluation of coated pellets of the three polymorphic forms of prazosin hydrochloride indicated a release dependence on the degree of crystallinity of the polymorphic form. XRD studies showed an increase in crystallinity of the drug after coating. DSC studies of coated beads revealed shifts in the melting endotherm of all three polymorphs in comparison with the pure drug suggesting a possible interaction between prazosin hydrochloride and the latex. SEM pictures revealed a uniform coat on the exterior and a distinct porous core. Optimized pellets of prazosin hydrochloride followed the Higuchi square-root model dissolution kinetics.

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